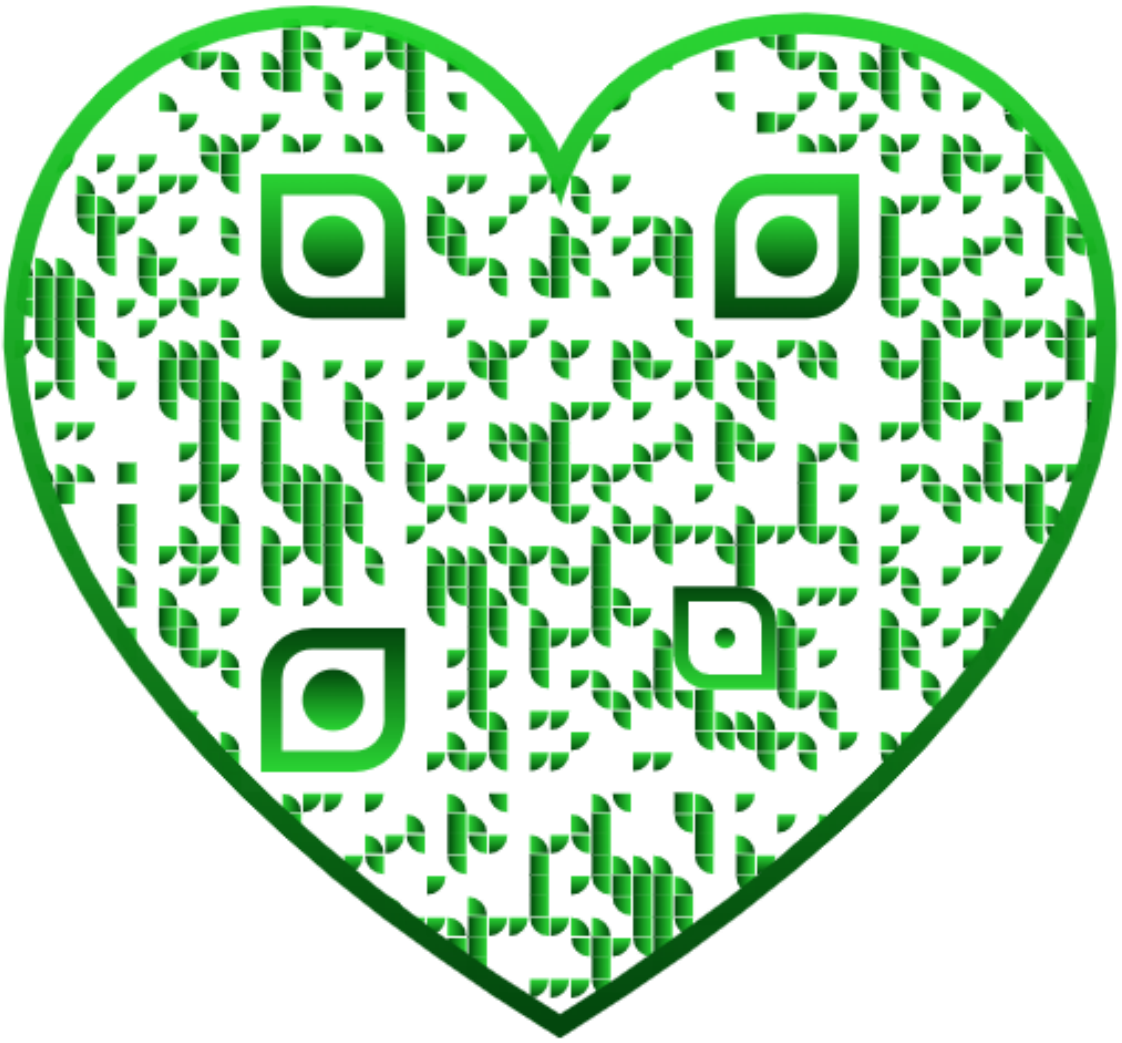
5. Diffusion and Dissolution



Introduction: Diffusion, Osmosis, Dialysis

- The mass transfer of a solvent or a solute forms a basis for many important phenomena in the pharmaceutical sciences.
- **Diffusion** ~ a spontaneous transfer of molecules from a region of higher concentration to a region of lower concentration.
  - It is a result of random molecular movement.

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- The theory of diffusion has been used:
  - In investigating the mechanism of drug transport.
  - To the design and development of various controlled/sustained release formulations.
- Diffusion can be studied by observing the flow the molecules through a barrier.

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- The passage of solute molecules through the barrier occurs:
  - Simple molecular diffusion (permeation) involves dissolution of the solute in the bulk membrane.
  - Passage through pores & channels (through solvent filled-pores of the membrane).
  - Diffusion through &/or between the fibrous membrane strands.

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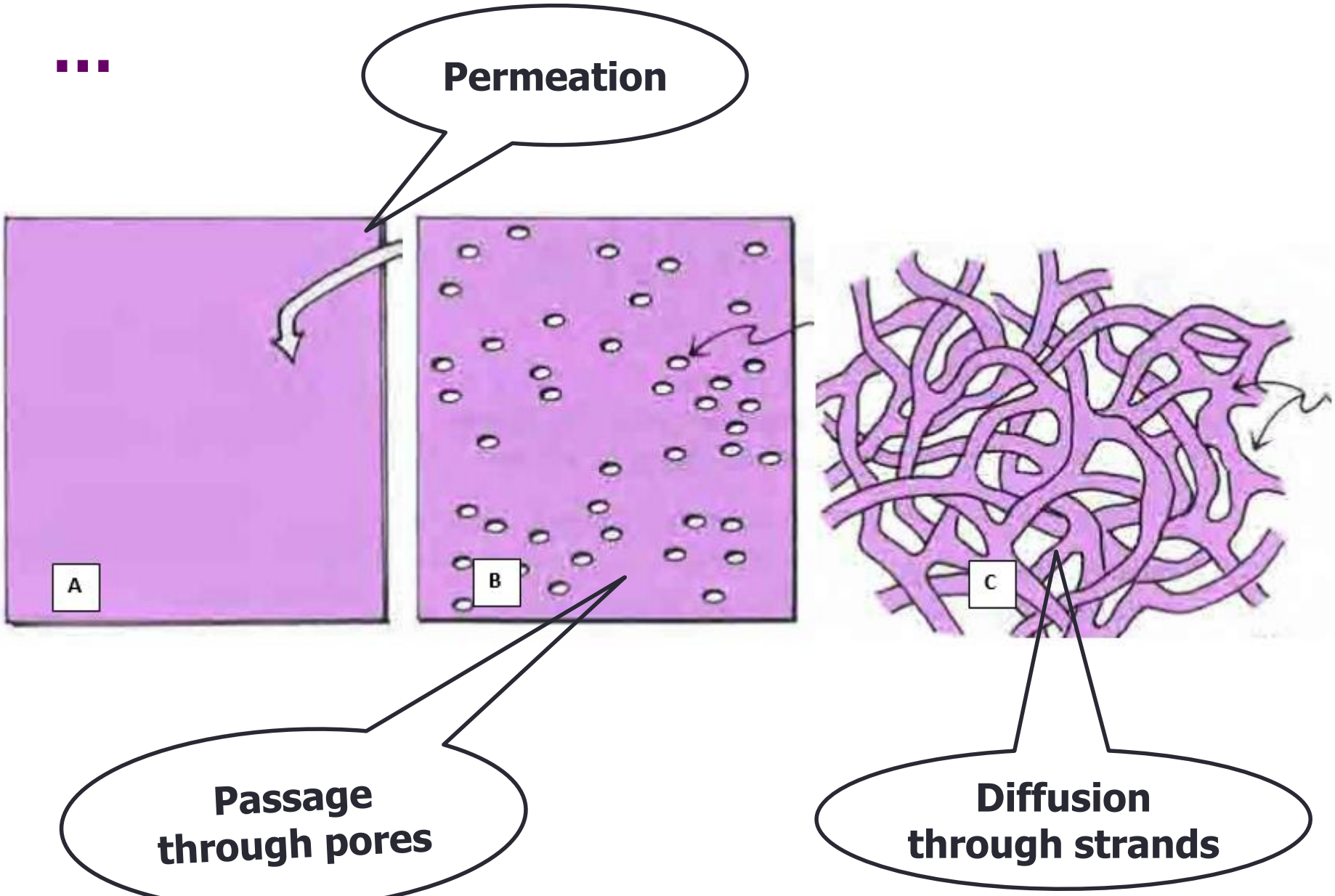
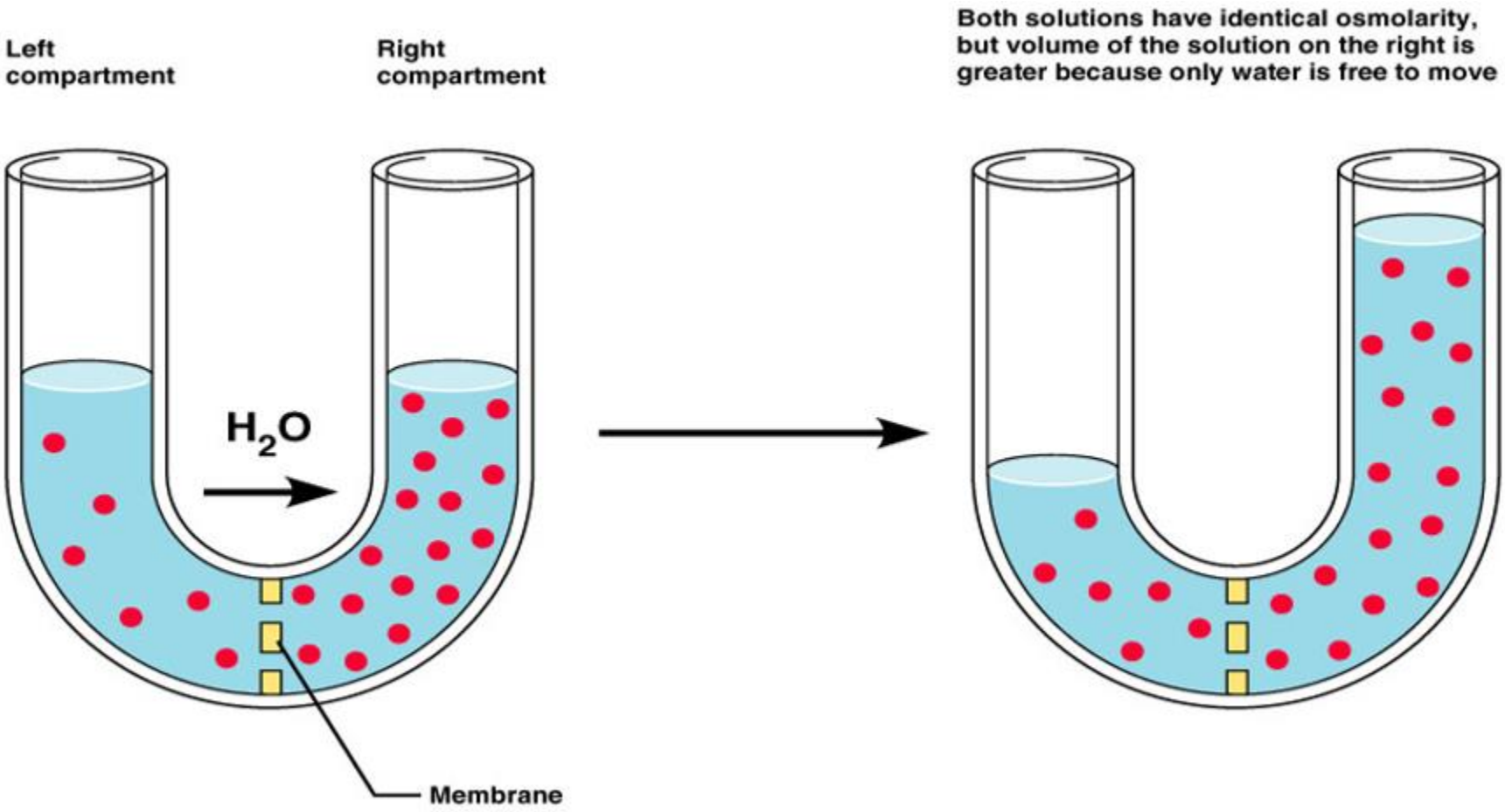

Permeation
A
B
C
Passage
through pores
Diffusion
through strands

...

- **Osmosis** ~ defined as movement of solvent across a selectively permeable membrane down its concentration gradient.
- Movement toward the solution containing the higher solute concentration.
  - This solution has a lower solvent concentration,
  - Movement continues until solvent concentrations and solute concentrations are the same on either side of the membrane (identical osmolarity).


Left compartment
Right compartment
H_2O
Membrane
Both solutions have identical osmolarity, but volume of the solution on the right is greater because only water is free to move

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- **Dialysis** ~ the process of separation of dissolved substances from a solution by allowing the solution to diffuse through a semipermeable membrane.
  - Read more (Medical application)

Drug Transport Systems

- Various nutrients and drugs are transported across the blood by various mechanisms:

1. Passive diffusion
2. Carrier mediated transport
   a) Facilitated transport
   b) Active transport
3. Co-transport
4. Vesicular transport

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Passive diffusion

- Major process for absorption of majority of drugs.
- Diffusion follows Fick's laws
  - The drug molecules diffuse from a region of higher concentration to a region of lower concentration till equilibrium is attained.
  - Rate of diffusion is directly proportional to the concentration gradient across the membrane.

- Factors affecting Passive diffusion:
  - Diffusion coefficient of the drug,
  - Thickness and surface area of the membrane,
  - Size of the molecule,
  - Concentration of the drug (concentration gradients),

...

- Characteristics of passive diffusion:
  - Down hill transport, and energy independent,
  - The greater the surface area & lesser the thickness of the membrane, the faster is the diffusion,
  - The greater the membrane/water partition coefficient, faster the diffusion,
  - Depends more or less on the square root of the molecular size of the drugs,
  - Equilibrium is attained when the concentration on either side of the membrane become equal.

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Carrier mediated transport

- Involves a carrier which binds **reversibly** with the solute molecules (drugs) to be transported.
- The carrier-drug complex transverses across the membrane to the other side where it dissociates to yield the solute molecule (drug) and carrier.
- The carrier then returns to its original site to accept a fresh molecule of solute (drug).

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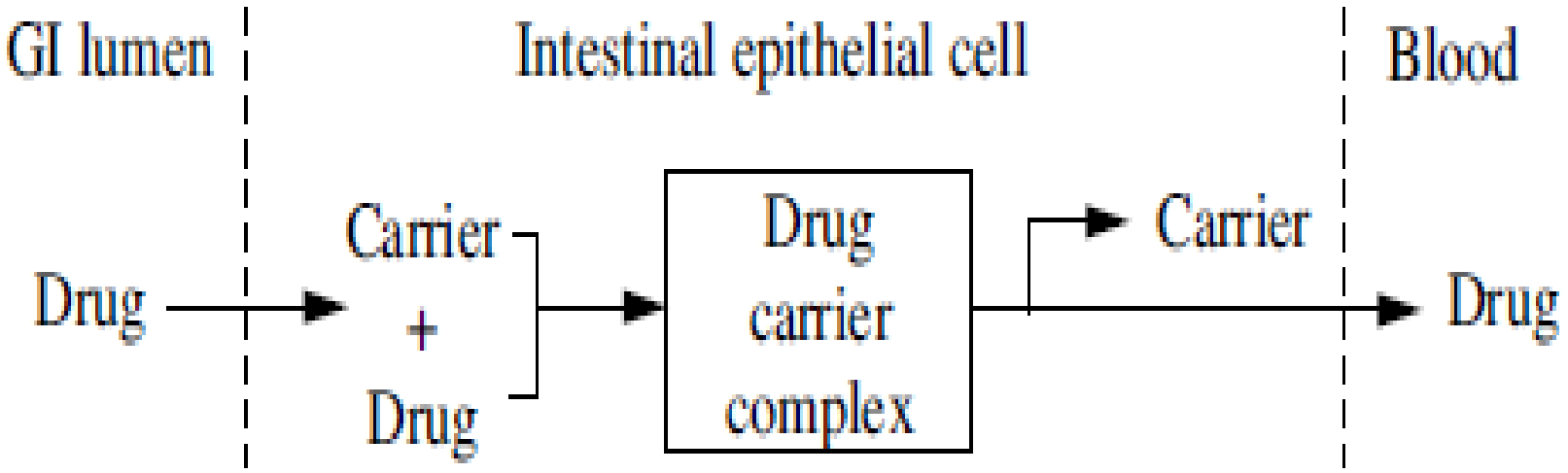
- Carrier-mediated absorption is saturable process.
- The maximum transport rate will be determined by:
  - Concentration of carrier molecules, and
  - The speed with which they can shuttle material across the membrane,
- Transport rate does not depend on the concentration of the molecules being transported.


GI lumen
Intestinal epithelial cell
Blood
Drug
Carrier
+
Drug
Drug
carrier
complex
Carrier
Drug

...

A) Facilitated transport

- Concentration gradient is the driving force.
- In this system, no expenditure of energy is involved (down-hill transport).
- The process is not inhibited by metabolic processes that interfere with energy production.
- The transport is facilitated by proteins.

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- Facilitated transport has a **limited** importance in the absorption of drugs.
  - E.g. Entry of glucose into RBCs & intestinal absorption of vitamins B1, B2 & B12.
  - An intrinsic factor (IF), a glycoprotein produced by the gastric parietal cells, forms a complex with vitamin B12 which is then transported across the intestinal membrane.

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B) Active transport

- Transport is against the concentration gradient (uphill transport).
- Since the process is uphill, energy is required.
- As the process requires expenditure of energy, can be inhibited by metabolic processes that interfere with energy production.

...

- Endogenous substances that are transported actively include sodium, potassium, calcium, iron, glucose, amino acids, and vitamins like niacin, pyridoxine.

- Drugs having structural similarity to such agents are absorbed actively

E.g. Pyrimidine transport system – absorption of 5 FU

L-amino acid transport system – absorption of methyldopa and levodopa

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Co-transport

- Transport in which the cells' ion concentration gradient is used as a secondary energy source.
  - The transport proteins are systems which couple the transport of an ion to that of another molecule.
  - If the ion and molecule move across the membrane in the same direction, the process is called as **symport**
  - If they are exchanged in opposite directions, the process is called as **antiport**.

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Vesicular transport (cytosis)

- Transport mechanism for the movement of large particles or macromolecules into and out of cells.
- Endocytosis and Exocytosis are the processes of moving macromolecules into and out of a cell, respectively.
- Pinocytosis - the engulfment of small solutes or fluid.
- Phagocytosis - the engulfment of larger particles or macromolecules.

Fick's Laws of Diffusion

Fick's first law

- The amount, M, of material flowing through a unit cross section, S, of a barrier in unit time, t, is known as the flux, J.

$$J = \frac{dM}{Sdt}$$

- The flux is also proportional to the concentration gradient, $\frac{dC}{dx}$

$$J = -D\frac{dC}{dx}$$

- D ~ Diffusion coefficient of a penetrant (the diffusant) (cm^2/sec)
- C ~ Concentration in g/cm^3
- X ~ distance in cm of movement perpendicular to the surface of the barrier
- Mass (gram or moles), S (cm^2), time (sec)
- The unit of J is g/cm^2sec

...

- Diffusion coefficient or diffusivity (D) is affected by:
  - Concentration,
  - Temperature,
  - Pressure,
  - solvent properties and
  - Chemical nature of the diffusant

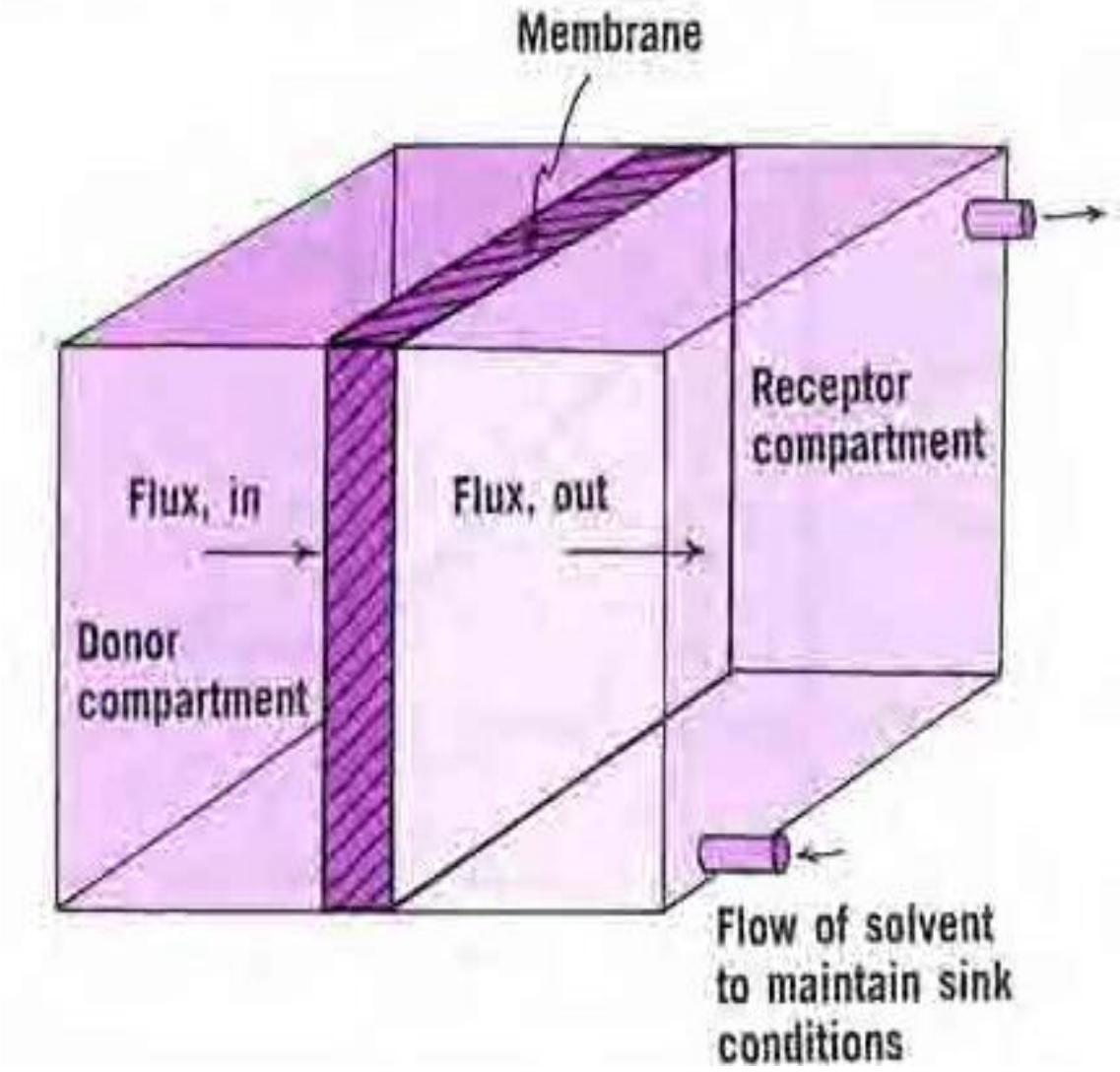
...

Fick's second law

- Emphasizes the change in the concentration with time at a definite location rather than the mass diffusing across a unit area of barrier in unit time.

- The diffusion equation is derived as follows.

  - The concentration, C, in a particular volume element changes as a result of net flow of diffusing molecules into and out of the region.


Membrane
Receptor compartment
Flux, in
Flux, out
Donor compartment
Flow of solvent to maintain sink conditions

...

- The concentration of diffusant in the volume element changes with time, $\frac{\Delta C}{\Delta t}$, as flux changes with distance, $\frac{\Delta J}{\Delta x}$, in the x direction, or

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x}$$

- Differentiating first law expression with respect to x,

$$-\frac{\partial J}{\partial x} = \frac{\partial^2 C}{\partial x^2}$$

...

- Through substitution the above equation will result in Fick's second law:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

- This last equation represents diffusion only in the x direction.

...

- Fick's second law states:

"the change in the concentration with time in a particular region is proportional to the change in the concentration gradient at that point in the system"

Non-steady state and Steady state diffusion

- **Non-steady state diffusion**
  - Refers to a diffusion process in which the concentration of diffusant in a given space is a function of time.
  - In this case, one should use Fick's second law to study the diffusion process.
  - Mathematically, this condition can be described as:

$$\frac{dC}{dt} \neq 0$$

- **Steady state (SS) diffusion**
  - When the amounts of diffusant enter and leave the given space at the same rate, the concentration of the diffusant in the given volume is a constant.
  - The concentration in the given space is independent of time.
  - Mathematically, this condition can be described as:

$$\frac{dC}{dt} = 0$$

...

- The Fick's second law can be written for steady state diffusion as:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} = 0$$

  - The concentration gradient across the membrane, dC/dx, is constant, signifying a linear relationship between concentration, C, and distance x.

  - In other words, the concentration gradient is a constant for diffusion at the steady state.

Lag time and burst effects

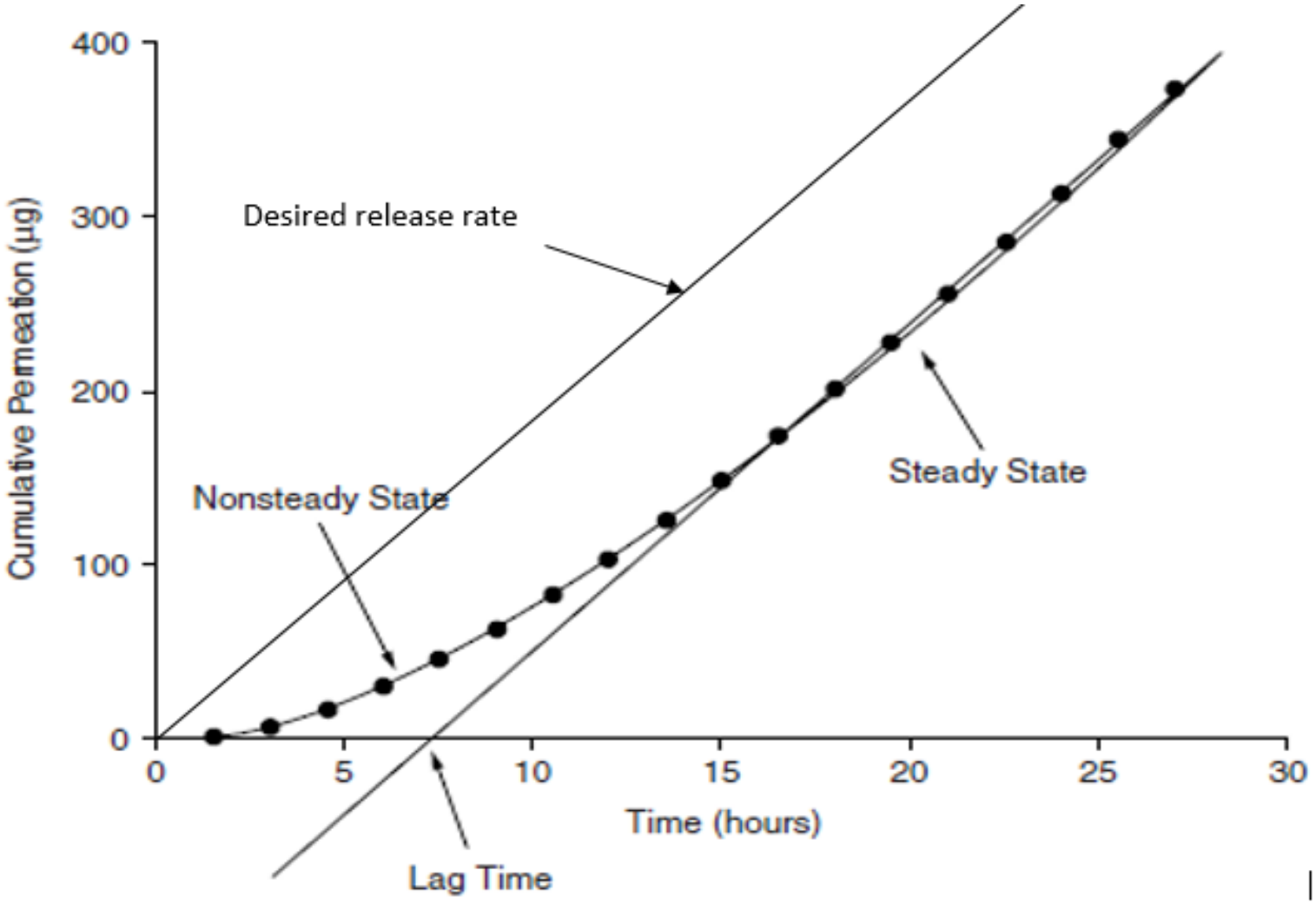
- **Lag time**
  - The time required for a diffusion to establish a uniform concentration gradient within the membrane that separates the donor and receptor compartments.
  - The time required to attain the steady state.

- The lag time ($\boldsymbol{t_L}$) is given by:

$$t_L = \frac{h^2}{6D}$$

- Where h is membrane thickness and D is diffusivity

- $\boldsymbol{t_L}$ may be obtained by extrapolating the steady state portion of the line to the time axis.


400
300
200
100
0
Cumulative Permeation (µg)
Desired release rate
Nonsteady State
Steady State
Lag Time
0
5
10
15
20
25
30
Time (hours)

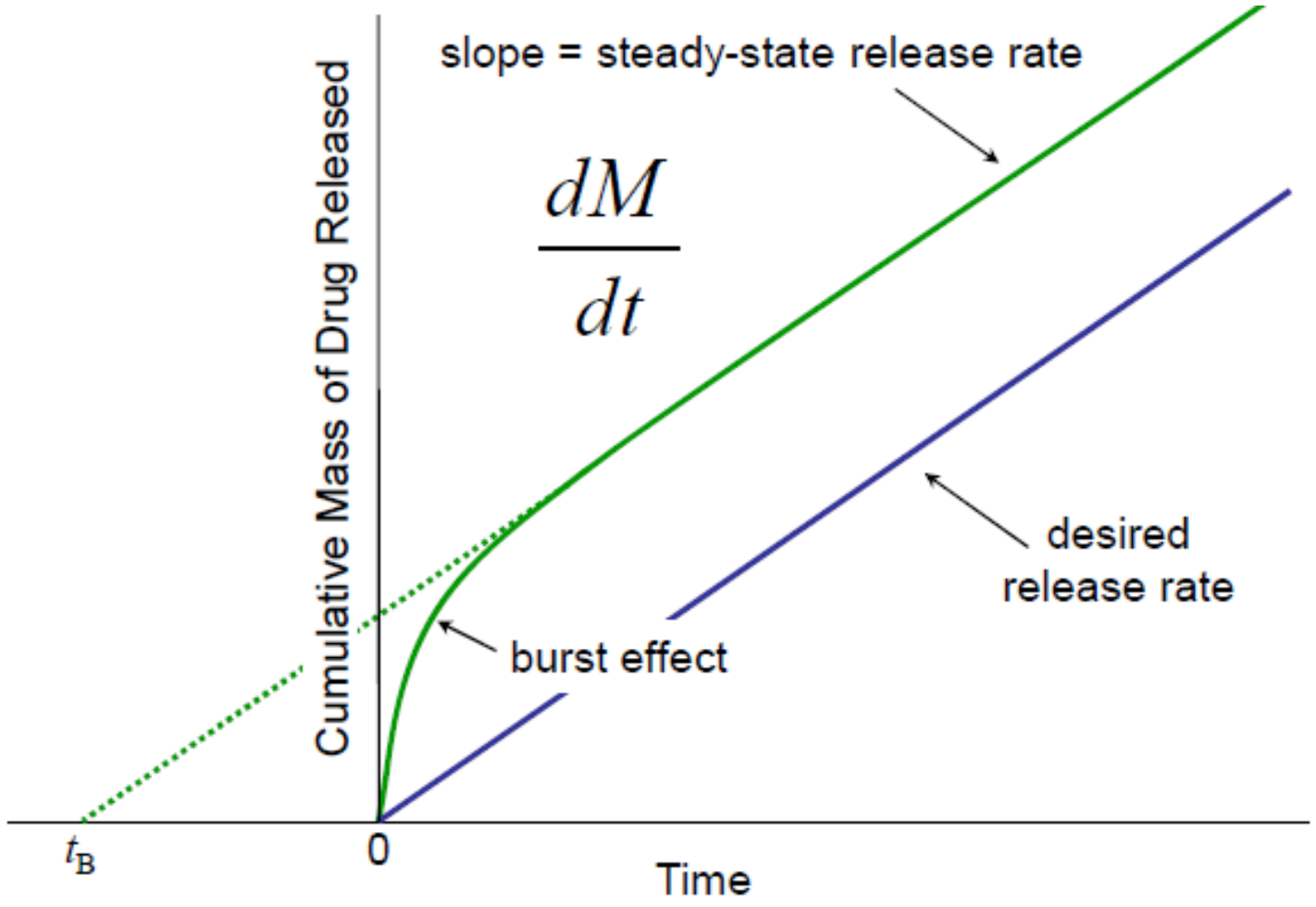
- **Burst effects**

  - Initial release of drug into receptor side is at a higher rate than the steady-state release rate.

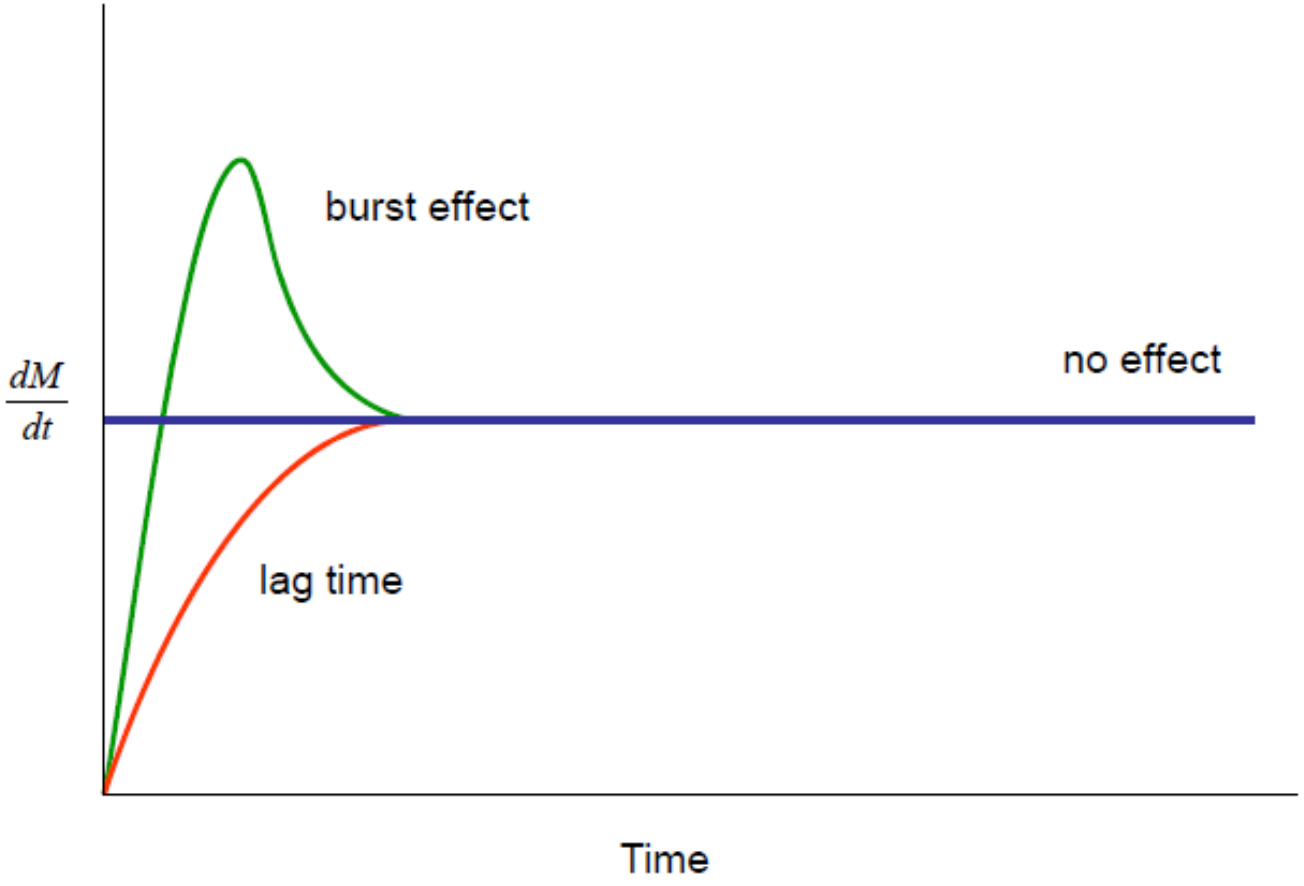
  - Burst effect may be expressed in terms of the diffusion coefficient and the membrane thickness.

$$t_B = \frac{h^2}{3D}$$

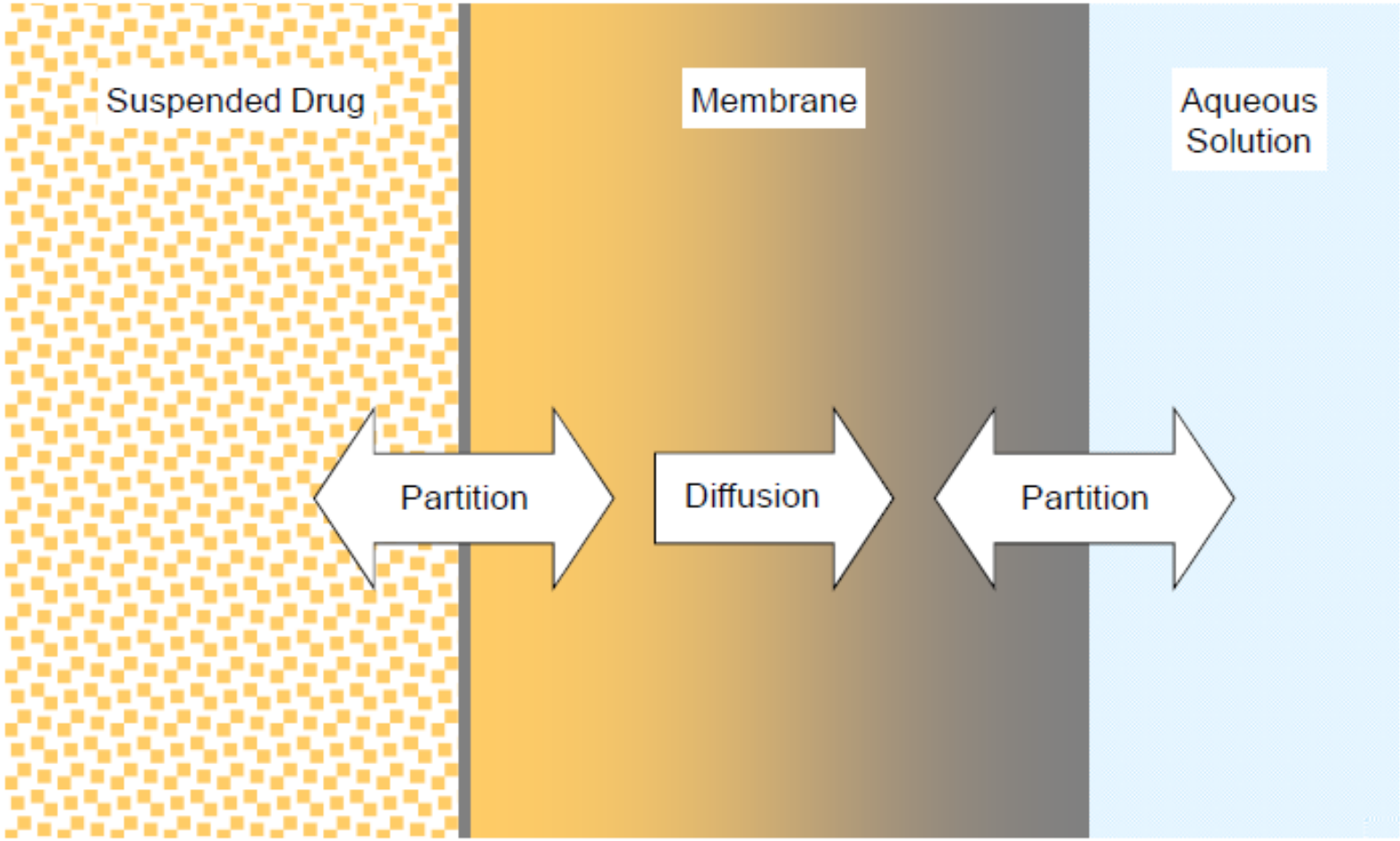
  - t_B may be obtained by extrapolating the steady state portion of the line to the time axis.


slope = steady-state release rate
$\frac{dM}{dt}$
Cumulative Mass of Drug Released
desired
release rate
burst effect
t_B
0
Time

- Burst effects Vs. Lag time



Diffusion through a membrane



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- Release of drug molecules through biological membranes occurs by a partition–diffusion–partition process.
  - Drug molecules must partition into the membranes,
  - Drug molecules entering the membrane must diffuse through membrane (concentration gradient),
  - Drug molecules in the membrane must then partition into aqueous medium.

- Types of membrane
  - **Impermeable membrane** - membrane though which nothing can pass.
  - **Freely permeable membrane** - any substance can pass through it.
  - **Selectively permeable membrane** - permits free passage of some materials and restricts passage of others.

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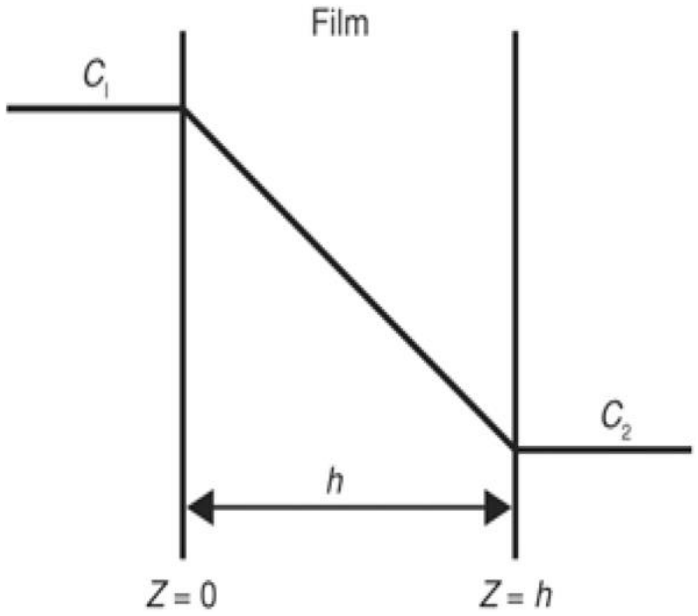
SS Diffusion and Diffusional resistance

- Diffusion occurs in the direction from the higher concentration to lower concentration.
- After sufficient time, SS is achieved and the concentrations are constant at all points in the film.
- At SS, Fick's second law becomes:

$$D\frac{d^2C}{dz^2} = 0$$



- Integrating the above equation using the conditions that at Z=0, C=C_1 and at z=h, C=C_2, yields:

$$J = \frac{D}{h}(C_1 - C_2)$$

...

- The term $\frac{h}{D}$ is often called the diffusional resistance, denoted by R, and the above flux equation can be rewritten as:

$$J = \frac{(C_1 - C_2)}{R}$$

- Resistance to diffusion is a fundamental scientific principle but permeability is used in more often in pharmaceutical sciences.
- Resistance and permeability are inversely related.

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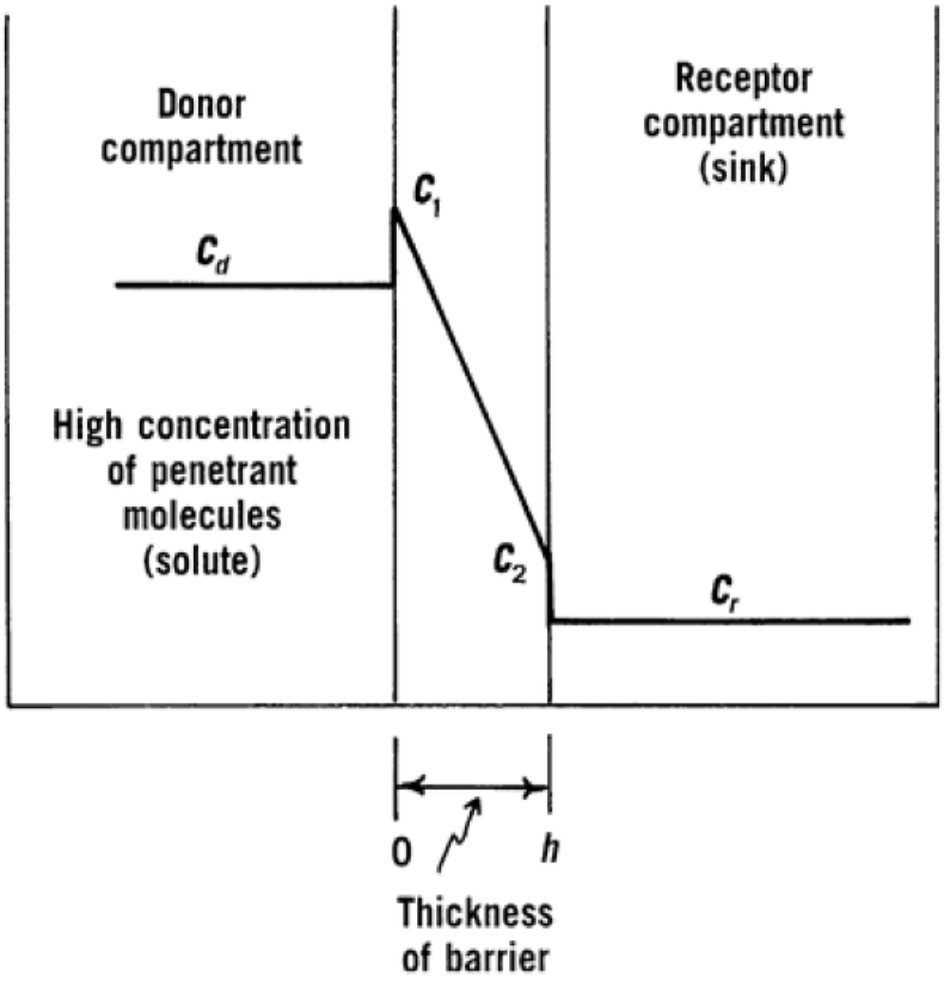
Permeability



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- For a membrane with cross-sectional area 'S' and thickness 'h' and the concentration in the membrane on the donor and on the receptor sides are C_1 and C_2 respectively, the Fick's first law can be written as:

$$J = \frac{dM}{Sdt} = D\left(\frac{(C_1 - C_2)}{h}\right)$$

- Where $\frac{(C_1 - C_2)}{h}$ approximates $\frac{dC}{dx}$.

...

- For steady state, the gradient $\frac{(C_1 - C_2)}{h}$ within the membrane assumed to be constant.
- C_1 and C_2 are not known but can be replaced by the partition coefficient multiplied by C_d or C_r
  - The distribution or partition coefficient is given by:

$$K = \frac{C_1}{C_d} = \frac{C_2}{C_r}$$

...

- **Replacing** for C_1 and C_2 in the equation $\frac{dM}{Sdt} = D\left(\frac{(C_1 - C_2)}{h}\right)$, and **rearranging**:

$$\frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h}$$

- If sink conditions hold in the compartment, $C_r = 0$, the above equation will reduce to:

$$\frac{dM}{dt} = \frac{DSKC_d}{h} = PSC_d$$

Where, $P = \frac{DK}{h}$, is permeability coefficient (permeability)

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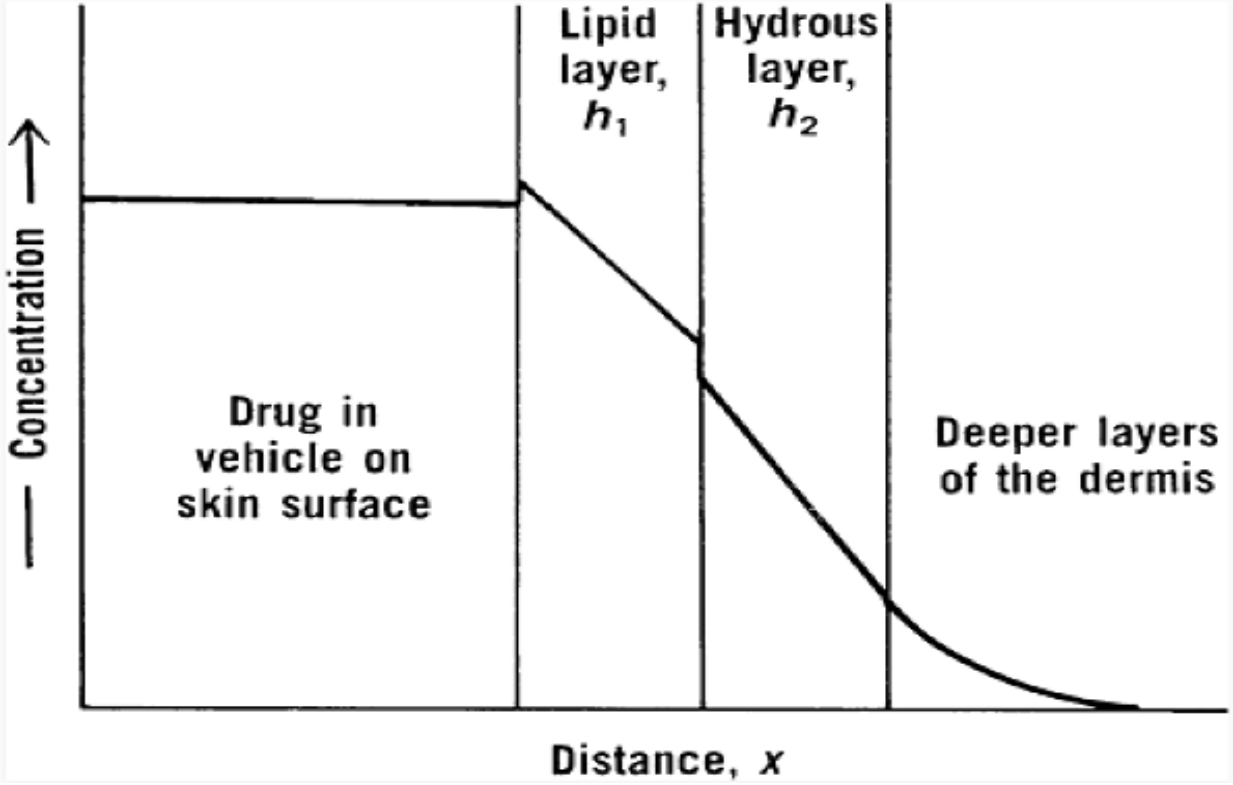
Multilayer diffusion

- This may be a case when,
  - Diffusion across biological barriers.
  - The passage of gaseous or liquid solute through the walls of containers and plastic packaging materials
  - The passage of a topically applied drug from its vehicles through the lipoidal and lower hydrous layers of the skin.



- Drug crossing lipoidal and the hydrous skin layers of thickness h_1 and h_2.

- The resistance, R, to diffusion in each layers is equal to the reciprocal of the permeability coefficient, Pi, of that particular layer.

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- For particular lamina **i**, P_i is given as:

$$P_i = \frac{D_i K_i}{h_i}$$

- And, the resistance to diffusion R_i for that particular layer:

$$R_i = \frac{1}{P_i} = \frac{h_i}{D_i K_i}$$

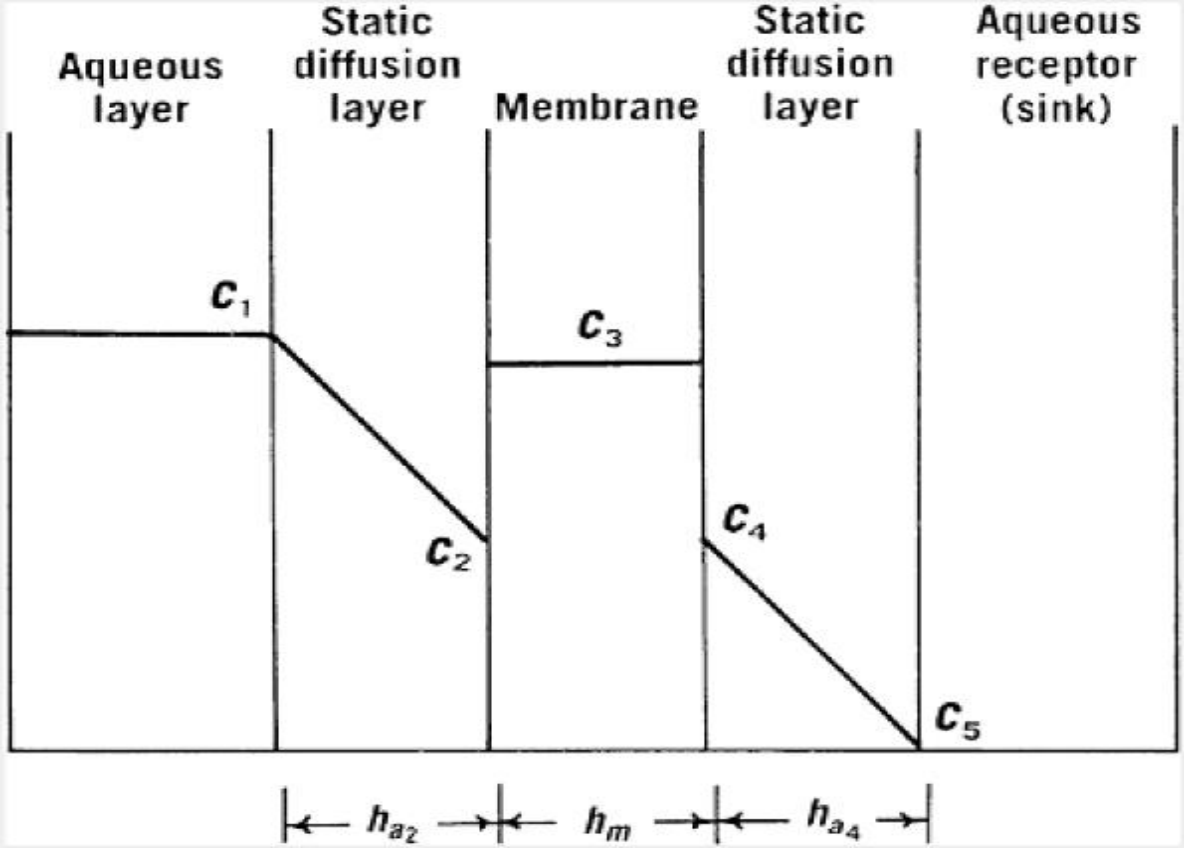
...

- The total permeability in terms of two layers can be expressed as:

$$P = \frac{D_1 K_1 D_2 K_2}{h_1 D_2 K_2 + h_2 D_1 K_1}$$

...

Membrane control and aqueous layer control diffusion



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- The permeability of the barrier, consisting of the membrane and the two static aqueous diffusion layers, is given by:

$$P = \frac{1}{R} = \frac{D_m K D_a}{h_m D_a + 2 h_a D_m K}$$

where $D_m \; and \; D_a$ are diffusion coefficient of the membrane and aqueous diffusion layer respectively; h_m and h_a being thickness of the membrane and aqueous diffusion layer respectively.

...

- The flux is simply the permeability multiplied by the concentration gradient:

$$J = P(C_1 - C_5)$$

  - The receptor serving as a sink (i.e. C_5=0), and the donor concentration C_1 is assumed to be constant.

  - Thus we have, $J = P.C_1$, and replacing for P:

$$J = \frac{D_m K D_a C_1}{h_m D_a + 2h_a D_m K}$$

...

Diffusion and the biological system

- Drug absorption by means of diffusion through the GI cells is governed by:
  - The state of ionization of the drug,
  - The drug's solubility and concentration in the intestine, and
  - Its membrane permeability.

...

- Most drug are weakly acidic or weakly basic.
- The fraction of drug that exists as ionized or unionized is determined in accordance Henderson-Hasselbalch relationship:

For weak acids: $$p^H = p^{K_a} + \log \frac{[A^-]}{[HA]}$$

For weak basis: $$p^H = p^{K_a} + \log \frac{[B]}{[BH^+]}$$

...

The pH-partition hypothesis

- Biological membranes being predominantly lipophilic are permeable to **unionized** species of a drug in preference to ionized species of the drug.
  - The rate of passive transport of the weak acid or base is related to the concentration of the drug that exists in the unionized form at the site of absorption.
- According to this hypothesis, the ionized forms of the drug cannot pass through the membrane.

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- From the Henderson-Hasselbalch relationship:
  - An acidic drug is absorbed from acidic solution if the p^H is lower than the drug p^{K_a},
  - Basic drug is absorbed from basic solution if the p^H is higher than the drug p^{K_a} since it will be in its unionized form.
- The pH-partition hypothesis has been found to be only partly applicable in the biological system.

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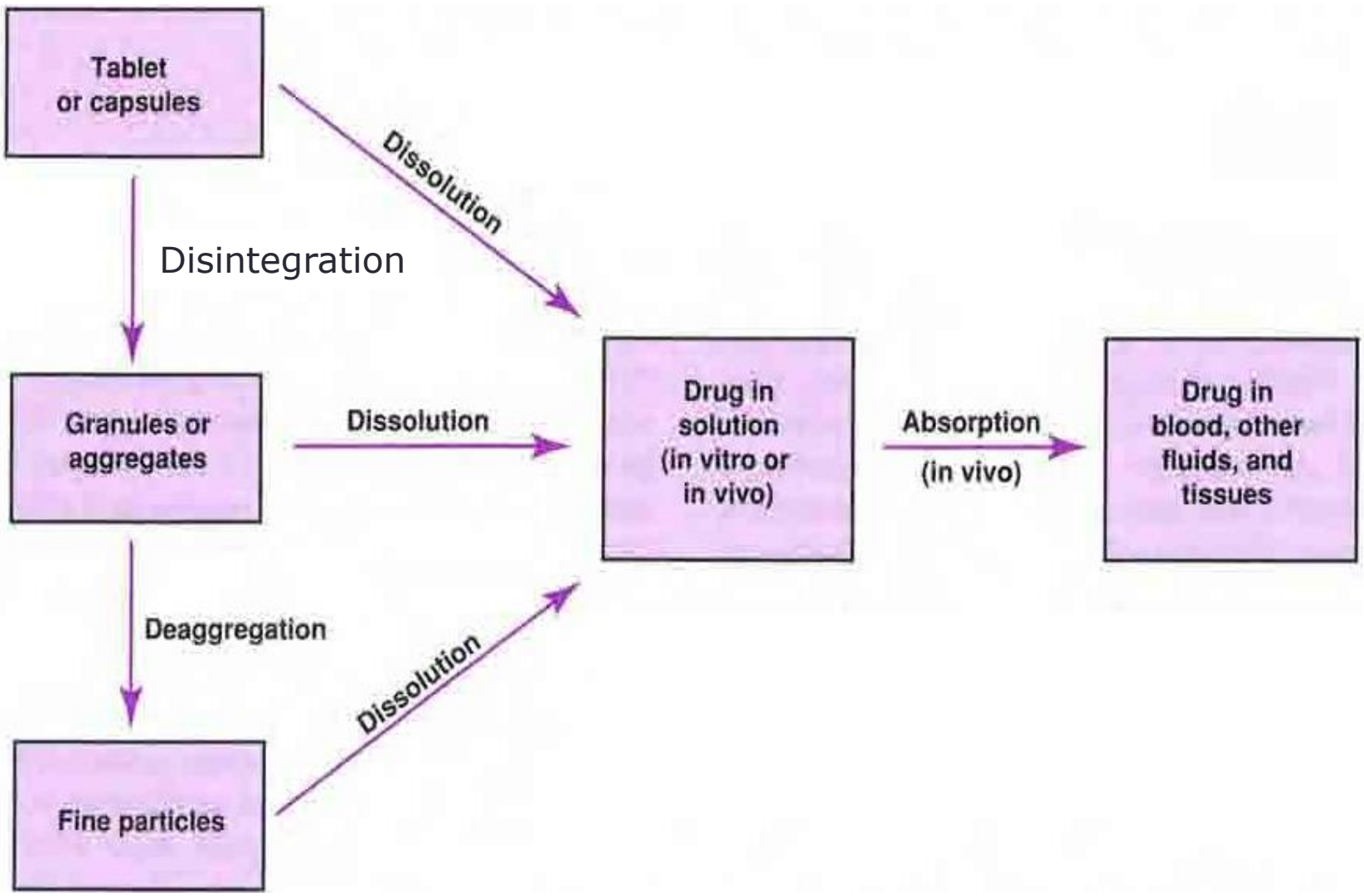
- This hypothesis does not consider:
  - Absorption of relatively small ionic and nonionic species through the aqueous pores and aqueous diffusion layer in front of the membrane.
  - Other complicating factors such as:
    - Metabolism of the drug in the GI membrane,
    - Absorption and secretion by carrier-mediated processes,
    - Absorption in micellar form and enterohepatic circulatory effects.

Dissolution

- Definition
  - Process by which solid phase (e.g. tablet or powder) enters into solution phase, or
  - Mass transfer from the solid surface to the liquid phase.
  - Rate of dissolution ~ amount of drug substance that goes in solution per unit time under standardized conditions of temperature and solvent composition.


Tablet or capsules
Dissolution
Disintegration
Granules or aggregates
Dissolution
Drug in solution (in vitro or in vivo)
Absorption
(in vivo)
Drug in blood, other fluids, and tissues
Deaggregation
Dissolution
Fine particles

...

- From the figure above, dissolution of the drug takes place from tablet, the disintegrated granules and from the fine particles.
- The effectiveness of the tablet in releasing the drug is dependent on:
  - The rate of disintegration and deaggregation, and
  - The rate of dissolution of the solid drug (more important)

...

- Most often the dissolution step is the slowest and hence the rate-controlling step in the bioabsorption of drugs of low solubility.

...

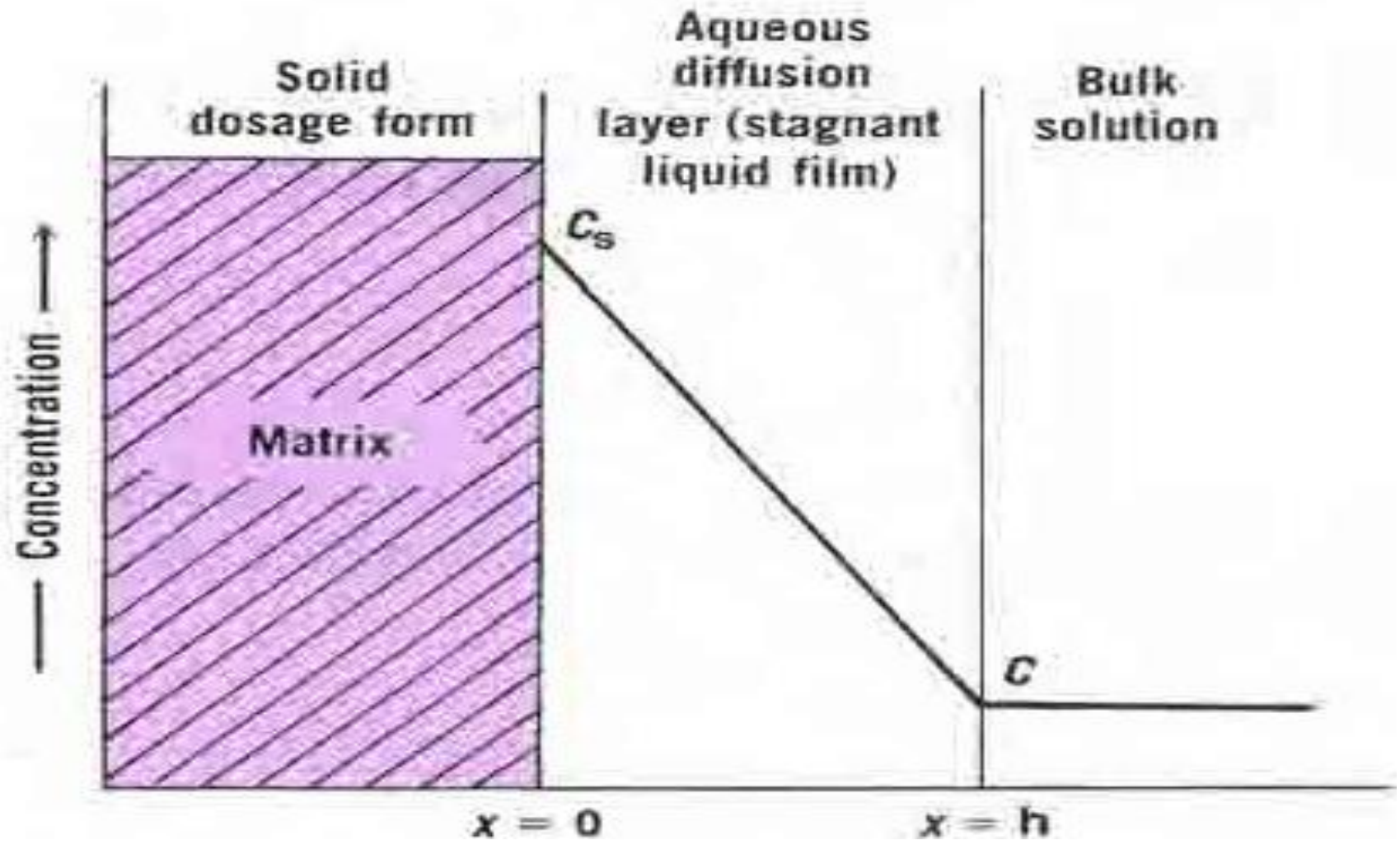
- The dissolution of a solid in a liquid may be regarded as being composed of two consecutive stages:

1) First is an interfacial reaction that results in the liberation of solute molecules from the solid phase.

   - Molecules of solid become molecules of solute in the solvent.
   - The solution in contact with the solid will be saturated (C_s).

2) Solute molecules migrate through the boundary layers surrounding the crystal to the bulk solution.

   - Movement from solid-liquid interface into the bulk.


Solid
dosage form
Aqueous
diffusion
layer (stagnant
liquid film)
Bulk
solution
C_s
Matrix
C
Concentration
$x = 0$
$x = h$

...

- Mass transfer takes place more slowly through the static or slow-moving layer,
  - This layer inhibits the movement of solute molecules from the surface of the solid to the bulk of the solution.
- The rate of dissolution is determined by the rate of the slower step.
  - Diffusion of dissolved solute across the static boundary layer of liquid that exists at a solid-liquid interface.

...

- The rate at which a solid dissolves in a solvent is quantitatively given by the **Noyes-Whitney equation:**

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C)$$

Or

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_s - C)$$

...

- Under 'sink' conditions, $C_s \gg C$, and the above equation will be reduced to:

$$\frac{dC}{dt} = \frac{DSC_s}{Vh}$$

D = diffusion coefficient of the solute (cm^2/s), S = the surface area of the exposed solid (cm^2), h = thickness of the diffusion layer (cm), Cs = the solubility of the solid (i.e the concentration of a saturated solution of the compound at the surface of the solid), C = concentrations of the solute at the bulk solution at time t, dC/dt = the dissolution rate, V = the volume of the solution.

...

- 'Sink' conditions may arise *in vivo* when a drug is **absorbed** from its solution in the GI fluids at a **faster** rate than it **dissolves** in those fluids from a solid dosage form.

- If $C > \frac{C_s}{10}$, then 'non-sink' conditions are said to be in operation.

- When C = Cs, the overall dissolution rate will be zero, as the dissolution medium is saturated with solute

...

- Limitation of Noyes-Whitney equation:
  - In the derivation of Noyes-Whitney equation, it was assumed that h and S are constant.
  - However,
    - S decrease as particle size decrease when solid undergoes dissolution.
    - Thickness of the static layer also altered by agitation.

- Assignment (Reading)
  - *In vitro* dissolution testing methods.

Application of the principles of Diffusion and Dissolution

Diffusion controlled Drug Delivery systems

- Polymers function as physical barriers to drug transport and hence control the rate of release of a drug when administered orally.

- Diffusion controlled systems are of two types:

1. Reservoir devices

2. Matrix devices.

- Reservoir devices
  - Drug release is believed to involve the following processes:
    - GI fluid penetrate the coating and the drug dissolves to produce a saturated solution,
    - The drug diffuses though the polymeric coating,
    - A fairly constant rate of drug release occurs if the concentration of drug in the core remains at saturation,
    - The release of solutes from polymeric drug delivery systems are based on Fick's first law of diffusion.

- Matrix Devices
  - A matrix device consists of an inert polymeric matrix in which a drug is uniformly distributed.
    - Drugs can be dissolved in the matrix
    - The drugs can be present as a dispersion
  - The state of presentation leads to different release characteristics.

...

Dissolution and Diffusion Controlled Systems

- In this system, the drug forms the core, which is surrounded by a partially water-soluble polymer.
- Drug release is triggered by the dissolution of the water-soluble part of the polymer membrane.
  - Diffusion of the drug through the holes or pores in the polymer.
- Achieved by incorporating water-soluble additives in the polymer coating.

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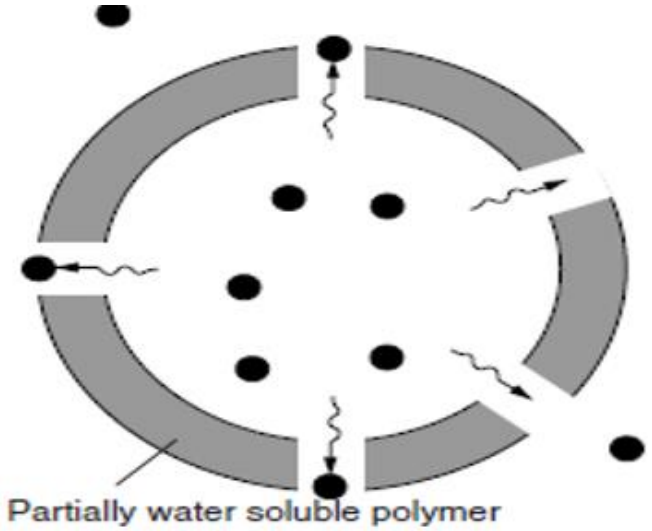
- When placed in an aqueous environment, the water-soluble additives (pore-formers) in the polymer coating dissolve to leave pores.



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- The kinetics of the release of drugs from dissolution-controlled systems is often described by the **Noyes-Whitney equation**:

$$\frac{dC}{dt} = \frac{DS}{hV}(C_s - C)$$

dC/dt is the dissolution rate; V is the volume of the solution; D is the diffusion coefficient; h is the thickness of aqueous diffusion layer; S is the surface area of the exposed solid; Cs is the saturated solubility of the drug; C is the concentration of the drug in the bulk solution.

...

Osmotic controlled drug release

- This type of delivery device has a semipermeable membrane that allows a controlled amount of water to diffuse into the core of the device filled with drug and osmotic agent.

- A water-sensitive component (osmotic agent) in the core can either dissolve or expand to create osmotic pressure.

  - And, push the drug out through a small delivery orifice.

...

- Constant release rate can be achieved from an osmotic pump system, since it relies simply on the passage of water into the system.
- The release rate of the device is affected by:
  - The amount of osmotic agent
  - Surface area and thickness of semipermeable membrane,
  - The size of the hole.

...

- The rate at which drug is pumped out of the osmotic system through the orifice is equal to the volume flow rate of water into the core multiplied by drug concentration at saturation:

$$\frac{dM}{dt} = \frac{dV}{dt} C_s$$

- Where,

$$\frac{dV}{dt} = \frac{AP}{h} \Delta\pi$$

...

- Therefore,

$$\frac{dM}{dt} = \frac{dV}{dt} C_s = \frac{AP}{h} \Delta\pi C_s$$

$\frac{dM}{dt}$ is the amount of drug delivered per unit of time (hours); $\frac{dV}{dt}$ is the volume flow rate; Cs is the concentration of the saturated solution; P is membrane permeability; A is semipermeable membrane surface area; h is thickness of the membrane; $\Delta\pi$ is osmotic pressure difference.